International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Tinospora cordifolia: An Antimicrobial and Immunity Enhancer Plant

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Abstract: ***Tinospora cordifolia or "Guduchi" is a well-known medicinal plant studied extensively since ancient times. This review article specifically describes the role of Tinospora cordifolia as an antimicrobial agent and as an immunity enhancer plant. The immunomodulatory potential of Tinospora cordifolia with specific references to extract and its isolated compounds along with the human trials is reviewed in this article. Also the probable use of Tinoposra in UTI infections is discussed over here.***

Keywords: *Tinospora cordifolia,* antimicrobial, immunomodulator, Guduchi, UTI

1. Introduction

Tinospora cordifolia (Willd.) Miers ex Hook.F. & Thoms. (Family: Menispermaceae) is an important drug of Indian Systems of Medicine (ISM) and used in medicines since times immemorial. *Tinospora cordifolia* (Guduchi) is one of the most versatile rejuvenative herb belonging to the family Menispermaceae. It is also called as 'Amrita or nectar of life', as it strengthens the immune system of the body and maintains the functions of its various organs in harmony [1]. In the ancient literature *T. cordifolia* preparations were used in fever, diabetes, dyspepsia, jaundice, urinary problems, skin diseases and chronic diarrhoea and dysentery. It has also been indicated to be useful in the treatment of heart diseases, leprosy, helmenthiasis and rheumatoid arthritis [2,3,4,5].

T. cordifolia and its phytochemicals are known and studied for its antimicrobial properties. In the last few years, a number of studies have been conducted in different countries to prove such efficiency [6]. *T. cordifolia* is well known for its immunomodulatory response. This property has been well documented by the scientists. A variety of compounds which are responsible for immunomodulatory activity are isolated and studied from the plant [7,8,9].

Urinary tract infections (UTl) are one of the most common infectious diseases caused by bacterial entry and multiplication along the normally sterile urinary tract. UTI can progress to become a complicated infection in an individual with functional, metabolic or structural abnormalities of the genitourinary tract. Recurrent UTI is also common with relapse or re-infection. *E.coli* is the commonest cause and other organisms involved are *Klebsiella*, *Proteus*, *Enterobacter*, *Citrobacter*, *Serratia* and *Pseudomonas*. UTI significantly impacts the quality of life of patients with a psychological burden because they live with the anxiety of sudden acute episodes. Synthetic antimicrobial agents are equally efficacious against UTI however, these drugs have limited therapeutic utility and the organisms rapidly develop resistance. Complicated UTIs normally require a longer course of antibacterial therapy that is associated with the various side effects [10,11,12,13]. This warrants the need of an alternative therapy with less side-effects or which can be used as an adjuvant therapy along with the standard line of treatment. With this view we here review the specific antimicrobial and immunomodulatory activity of *T. cordifolia* and its relevance in urinary tract infections.

2. *Tinospora cordifolia:* Anti-microbial activity

Plant extracts of *Tinospora cordifolia* (TC) have been reported to have potential against microbial infections. The anti-bacterial activity of *Tinospora cordifolia* extracts has been assayed against various Gram positive and Gram negative organisms. The antimicrobial activity of TC stem extracts was investigated against bacteria causing UTIs viz. uropathogens, *Escherichia coli* and *Staphylococcus aureus*. The study conducted using disc diffusion method showed that all three solvent extracts of TC reveal different antibacterial activity against both uropathogenic isolates with decreasing order as ethanolic (maximum) > methanolic (moderate) > aqueous (poor)[6].

The MIC value of TC is also studied for crude ethanolic extract of TC and isolated compound [(5R, 10R)-4R, 8R-Dihydroxy-2S, 3R:15, 16-diepoxycleroda-13(16), 17, 12S, 18, 1S-dilactone]. The plant showed good antibacterial and antifungal activity against tested microbes. The MIC values recorded for extract were: *E.coli* (1.25 mg/ml), *Proteus vulgaris* (0.315 mg/ml) and *S.aureus* (0.315 mg/ml) and the compound inhibited the growth of *B.subtilis* (200 µg/ml), *E.faecalis* (125 µg/ml), *E. coli* (200 µg/ml) and *P. vulgaris* (125 µg/ml) [14]. In another study the antibacterial effect of TC stem methanol extract on *Escherichia coli*, *Staphylococcus aureus* and *Staphylococcus albus* was studied. The MIC value obtained was *Escherichia coli* 2.5 mg/ml, *Staphylococcus aureus* 5.0 mg/ml and *Staphylococcus albus* 7.5 mg/ml [15].

The antibacterial activity of TC is being proved in clinical isolates as well. Study using urinary pathogens viz., *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Pseudomonas aeruginosa* showed that ethanol extract of leaf of TC showed greater inhibitory action than other tested extracts (aqueous and chloroform) [16,17].

In an experiment done with hot methanol extract of TC, the plant showed considerable antibacterial activity. Maximum antibacterial activity of hot and cold methanol extracts was exhibited against *Staphylococcus aureus* followed by

Shigella dysenteriae, Escherichia coli and *Pseudomonas aeruginosa* [18].

In *in vitro* antimicrobial activity of TC, hydroalcoholic extract of stem was prepared by maceration technique. Effective antimicrobial activity against all the organisms, viz *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas sp*, *Proteus vulgaris*, *Enterobacter faecalis*, *Salmonella typhi*, *Aspergillus niger, Aspergillus fumigates, Mucor* sp and *Pencillium* was obtained [19,20,21].

Antibacterial activity of silver nanoparticles prepared from TC against multidrug resistant strains was studied. The silver nanoparticles of stem of TC showed the zone of inhibition ranges from 10 ± 0.58 to 21 ± 0.25mm. The MIC of AgNPs was found to be 6.25 to 200 µg/ml against *Pseudomonas aeruginosa*. Silver nanoparticles from TC possess very good antibacterial activity which may make them a potent source of antibacterial agent [22].

These studies show that *Tinospora cordifolia* possesses potential antimicrobial activity against uropathogens and can be used in UTI infections.

3. *Tinospora cordifolia:* Immunomodulatory Activity

Tinospora cordifolia (TC) has been studied extensively for its immunomodulation properties. TC has been shown to modulate phagocytosis, activate macrophages and various cytokines. TC extract and compounds have been studied by various scientists for immunomodulatory activity in experimental models and human studies as well.

4. Immunomodulatory activity of *Tinospora cordifolia* extract

Immunomodulatory activity of *Tinospora cordifolia* extract is being studied by various scientists in *in vitro* assays. The positive effect of TC, on macrophage activation was studied using J774A cells. The direct drug treatment of J774A cells showed activation as enhanced secretion of lysozyme by macrophage cell line J774A on treatment with TC and lipopolysacharide was observed. The enhanced inhibitory effects of TC (direct effect) and TC treated cell supernatant (indirect effect) on the bacteria (*E. coli*) indicated the susceptibility of bacteria. This study shows the potential significance of TC to be used as an immunomodulator for activation of macrophages [23].

In another study, the aqueous extract of TC exhibited boosting of phagocytic ability of macrophages, remarkable enhancement in nitric oxide production by stimulation of splenocytes and macrophages. The extracts were investigated for their effect on the cytokine profile (IL-6) by ELISA. Splenocytes cultured in low concentration of TC, as low as 1.56 µg/ml, produced significantly higher levels of IL-6as compared to un-stimulated cells. This study reveals the multifaceted immunomodulatory potential of TC [24].

The immunomodulatory activity of different extracts, fractions and isolated compounds of TC in relation to phagocytosis and reactive oxygen species production in human neutrophil cells was investigated using the PMN phagocytic function studies, NBT, NO and chemiluminescence assay. The ethyl acetate, water fractions and hot water extract exhibited significant immunomodulatory activity with an increase in percentage phagocytosis [25].

The protective effect of TC as compared to gentamicin in *E. coli* induced peritonitis was studied. Pretreatment with TC or gentamicin reduced mortality in mice injected with 1 x 10(8) *E. coli intraperitoneally* from 100% in controls to 17.8% and 11.1% respectively. This was associated with significantly improved bacterial clearance as well as improved phagocytic and intracellular bactericidal capacities of neutrophils in the TC treated group [26].

A study was performed to elucidate the possible mechanism of action for immunomodulatory activity of TC. The authors measured CFUGM-Colony forming units of the granulocyte macrophage series in serum of mice treated with TC. It was found that 10 days treatment with TC (100 mg/ kg/d) induced a significant ($p < 0.01$) increase in the number of CFUGM(255 +/49.32vs 38.51 +/9.98).This suggests activation of macrophages by TC leads to increase in GMCSF which leads to leucocytosis and improved neutrophil function [27].

Effect of TC extract on modulation of hepatoprotective and immunostimulatory functions in carbon tetrachloride (CCl4) intoxicated mature rats was studied. Treatment with TC extract (100 mg/kg body weight for 15 days) in CCl4 intoxicated rats was found to protect the liver, as indicated by enzyme level in serum. A significant reduction in serum levels of SGOT, SGPT, ALP, bilirubin were observed following TC treatment during CCl4 intoxication. Treatment with TC extract also deleted the immunosuppressive effect of CCl4, since a significant increment in the functional capacities of rat peritoneal macrophages (PM phi) was observed following TC treatment. The results suggest that treatment by TC extract may be the critical remedy for the adverse effect of CCl4 in liver function as well as immune functions [8].

The antiangiogenic activity of TC was studied using *in vivo* as well as *in vitro* models. Analysis of the serum cytokine profile showed a drastic increase of proinflammatory cytokines such as IL1beta, IL6, TNF alpha, granulocyte monocyte colony stimulating factor (GMCSF) and the direct endothelial cell proliferating agent, vascular endothelial cell growth factor (VEGF) in the angiogenesis induced control animals. Administration of TC extract could differentially regulate these cytokine's elevation. The differential regulation was further evidenced by the increased production of antiangiogenic agents IL2 and tissue inhibitor of metalloprotease1 (TIMP1) in the B16F10 injected, extract treated animals. Here, the observed antiangiogenic activity of the plant was thought to be related, at least in part, to the regulation of the levels of these immune cytokines and growth factors in the blood of the angiogenesis induced

animal. This study further potentiates the immunomodulatory role of TC [28].

The effect of TC, with proven hepatoprotective activity, was evaluated on Kupffer cell function, using carbon clearance test as a parameter. TC extract showed significant improvement in Kupffer cell function and a trend towards normalization [29]. The effect of TC on the proliferation and myeloid differentiation of bone marrow hematopoietic precursor cells was studied in mice model of Dalton's lymphoma.TC treated cells showed enhanced bone marrow proliferation and colony forming ability. Also an increase in count of bone marrow derived macrophages, IL1and TNF was observed. This study indicates that the TC can influence the myeloid differentiation of bone marrow progenitor cells and the recruitment of macrophages in response to tumor growth in situ [30].

Effect of herbal immunostimulant diet prepared using *Tinospora*, *Picrorhiza kurooa* and *Eclipta alba* extracts was studied against shrimp viral pathogenesis. The shrimps fed on immunostimulant diet significantly ($P<0.0001$) had more survival (74%) rate and reduction in the viral load as compared to control diet. Also the better performance of haematological, biochemical and immunological parameters was found in the immunostimulant incorporated diets. This study further proves the immunostimulant property of TC [31].

5. Immunomodulatory activity of compounds isolated from *Tinospora cordifolia*

Seven immunomodulatory active compounds belonging to different classes were isolated and characterised from TC. All the compounds showed significant enhancement in phagocytic activity and increase in nitric oxide and reactive oxygen species generation. This indicates that the immunomodulatory activity of TC may be attributed to the synergistic effect of group of compounds (25). An arabinogalactan isolated from the dried stems of TC showed polyclonal mitogenic activity against Bcells [32].

G14A, a compound from the stem of TC extract inferred 100% protection against lipopolysaccharide (LPS) induced mortality in mice. G14A binds to the murine macrophages leading to their activation and reciprocally inhibits binding of LPS to macrophages. An increase in serum IL1beta, IL6, IFN gamma levels and decrease in that of IL10 and TNF alpha was observed following challenge with LPS in mice pre-treated with G14Aas compared to the controls. In addition, G14Aalso modulated the release of nitric oxide by murine macrophages. Thus G14A appeared to induce tolerance against endotoxic shock by modulation of cytokines and nitric oxide [33].

The active principles of TC were found to possess anti complementary and immunomodulatory activities. Humoral and cell mediated immunity were dose dependently enhanced and macrophage activation was achieved by the studied compounds viz. Syringin (TC4), cordiol (TC7), cordioside (TC2), and cordiofolioside A (TC5) [34].

The antioxidant activity of an arabinogalactan polysaccharide isolated from TC showed good protection against iron mediated lipid peroxidation of rat brain homogenate as revealed by the thiobarbituric acid reactive substances (TBARS) and lipid hydroperoxide (LOOH) assays. The polysaccharide also provided significant protection against gamma ray induced damage [9].

6. *Tinospora cordifolia:* Clinical study as an Immunomodulator

Effect of TC as an immunomodulator adjuvant therapy was studied in diabetic ulcers in a prospective double-blind, randomized controlled study in 50 patients for over 18 months. The authors studied its influence on parameters/determinants of healing, on bacterial eradication and on polymorphonuclear phagocytosis. Diabetic patients with foot ulcers on TC as an adjuvant therapy showed significantly better final outcome with improvement in wound healing. Reduced debridements and improved phagocytosis were statistically significant, indicating beneficial effects of immunomodulation for ulcer healing [35].

The effect of TC, on surgical outcome in patients with malignant obstructive jaundice was evaluated. Thirty patients were randomly divided into two groups, matched with respect to clinical features, impairment of hepatic function (as judged by liver function tests including anti pyrine elimination) and immunosuppression (phagocytic and killing capacities of neutrophils). Group I received conventional management, ie vitamin K, antibiotics and biliary drainage; Group II received TC (16 mg/kg/day orally) in addition, during the period of biliary drainage. The phagocytic and killing capacities of neutrophils normalized only in patients receiving TC (28.2 +/5.5%and 29.47 +/6.5%respectively). TC was shown to improve surgical outcome by strengthening host defences [36].

7. Conclusion

Tinospora cordifolia possesses antimicrobial activity specifically against UTI pathogens. A wide spectrum of organisms is studied and Tinospora has shown activity against most of the major uropathogens. Tinospora is also studied by various scientists for its immunomodulatory activity. Tinospora enhances the immune potential by activating macrophages and other immune cells like interleukins and TNF factors. The immune modulating potential of Tinospora is proved for extract and the compounds isolated from this plant. Some human studies have further potentiated the active role of Tinospora as an antimicrobial and immune enhancer plant.

In UTI the host defence of an individual is impaired and microorganisms invade the urinary tract. In such cases Tinospora can act as an immunomodulator and help eliminate the pathogens and eradicate the infection by enhancing the immune system of the patient. Further human studies on large scale are in need to place *Tinospora cordifolia* as an important plant in development of plant based medications.

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